REMARKS

The amendments to the specification and claims find support in the specification and claims as filed. Support for the addition of SEQ ID NOs:3, 4 and 5 to the sequence listing may be found, for example, at page 18, paragraph 53.

The amendments to the claims find support in the specification and claims as originally filed. Support for the claim amendments adding the words "wherein the amino acid sequence of said modified form of an Aequorea wild-type GFP polypeptide is at least 95% homologous to the amino acid sequence of SEQ ID NO:2" may be found, for example, at page 10, paragraph 33. Amendments to the claims deleting the words "derived from" or replacing the words "derived from" with "of" find support in the specification, for example, at page 6, paragraph 24. Other claim amendments correct minor typographical errors.

No new matter is added by way of the amendments to the specification, sequence listing, or claims.

Claims 1-23 were pending in the application, with Claims 16-23 withdrawn from consideration pursuant to a Restriction Requirement, so that Claims 1-15 were examined in the Office Action. With the present amendment, Claims 16-23 have been canceled. Claims 1-15 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed had possession of the claimed invention; and under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification. Claims 1 and 2-15 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-15 have been rejected under the judicially created doctrine of obviousness double patenting, as allegedly being unpatentable over Claims 1-64 of U.S. Patent Serial No. 5,777,079 and over Claims 1-5 of U.S. Patent

Serial No. 6,066,476. Claims 1, 13 and 14 stand objected to as requiring minor typographical corrections.

Applicants respectfully traverse the rejections as discussed below.

The Rejections under 35 U.S.C. §112, First Paragraph

Claims 1-15 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention, and as allegedly not being enabled by the specification.

The Examiner states "The use of open language such as "comprises" results in the claims encompassing any structure as long as said structure comprises the above mutations." However, as amended, the claims require that the claimed compositions of matter comprise a modified form of an Aequorea wild-type GFP polypeptide, which has an amino acid sequence having at least 95% homology to the amino acid sequence of SEQ ID NO:2, and which, upon oxidation and cyclization of amino acid residues in the modified form corresponding to positions 65 to 67 of wild-type GFP polypeptide sequence (SEQ ID NO:2), forms a fluorescent product exhibiting a different excitation and/or emission spectrum from a corresponding product of the wild-type GFP polypeptide sequence.

Applicants thank the Examiner for her acknowledgement that the specification is "enabling for a modified GFP comprising the amino acid sequence that differs from SEQ ID NO:2 by only mutations S202F/T203I, I167V/T. S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K OR S65A/C/T/L/V/I." The claims, as currently amended, require that the amino acid sequence of the modified GFP polypeptide have at least 95% homology to the amino acid sequence of SEQ ID NO:2, and that the modified GFP yield a fluorescent product with the recited functional properties.

Applicants submit that the specification enables GFP variants closely related to the wild-type GFP SEQ ID NO:2. The claims provide bounds for relatedness, in that the claims require that the modified GFP:

have an amino acid sequence with at least 95% homology to the amino acid sequence of SEQ ID NO:2;

fluoresce upon oxidation and cyclization of amino acid residues in the modified form corresponding to positions 65 to 67 of SEQ ID NO:2; and

exhibit a different excitation and/or emission spectrum from a corresponding product of the wild-type GFP polypeptide sequence.

The specification provides enabling disclosure for substitution of amino acids (see, *e.g.,* pages 9 and 10, paragraphs 32 and 33). Furthermore, techniques for amino acid substitution and analysis of homology are widely known in the art. Methods for the assessment of biological activity (emission and excitation) are enabled by the specification, including the Examples. The specification provides enabling disclosure for different excitation and/or emission spectra (see, *e.g.,* pages 6 and 7, paragraphs 24-26, and page 9, paragraph 31). Thus, one of ordinary skill in the art would be able to make and use the claimed invention commensurate with the claims.

In addition, in view of the extensive disclosure, and of the required 95% homology to the amino acid sequence of SEQ ID NO:2, applicants submit that undue experimentation would not be required to practice the invention. As discussed above, techniques for amino acid substitution and analysis of homology are widely known in the art, and the specification provides enabling disclosure for substitution of amino acids (see, *e.g.,* pages 5 and 6, paragraph 23-25 and pages 9 and 10, paragraphs 32 and 33) and for the assessment of fluorescence and altered spectral characteristics (*e.g.,* pages 6 and 7, paragraphs 24-26, and page 9, paragraph 31). Applicants disclose that there is "surprising tolerance for substitution" at Tyr 66 (page 7, paragraph 27) and discuss other substitutions of the sequence. Thus, the specification does establish regions of the protein structure which may be modified without effecting

the requisite activity, the general tolerance to modification. Within the narrow limits required to maintain at least 95% homology to SEQ ID NO:2, and known strategies for amino acid substitution, one of skill in the art would be able to modify the amino acids in the expectation of obtaining the desired biological function. The Examiner has said that "the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful." However, as discussed above, the possible choices are not infinite. In addition, the many examples of the specification, and the limited number of possible substitutions given the requirement that at least 95% homology to SEQ ID NO:2 must be maintained, applicants submit that the specification provides sufficient guidance as to which of the possible choices is likely to be successful.

Accordingly, the specification being enabling for a modified GFP comprising the amino acid sequence that differs from SEQ ID NO:2 by specified mutations, and being enabling for a modified GFP that differs from SEQ ID NO:2 by less than 5% as measured by amino acid sequence homology, and enabling one of ordinary skill in the art to practice the invention without undue experimentation, applicants submit that the rejection of Claims 1-15 under 35 U.S.C. §112, first paragraph, is overcome.

The Rejections of Claims 1-15 under 35 U.S.C. §112, Second Paragraph

Claims 1 and 2-15 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter applicants regard as the invention. The Examiner suggested that the term "derived" in claim 1 renders the claim unclear, and renders its dependent claims unclear as well.

As amended, Claim 1 does not recite "derived from" but instead recites "a modified form of an Aequorea wild-type GFP polypeptide" and "a fluorescent product exhibiting a different excitation and/or emission spectrum from a corresponding product of the wild-type GFP polypeptide sequence."

A GFP has a chromophore "which is generated by cyclization and oxidation of the protein's own Ser-Tyr-Gly sequence at positions 65-67" (page 1, paragraph 4). As discussed in the specification at page 6, paragraph 24, "The fluorescent product derived from a wild-type or modified GFP polypeptide sequence is no longer strictly speaking a simple polypeptide after oxidation and cyclization; however, reference is sometimes made for sake of simplicity herein to the polypeptide (*e.g.*, "wild-type GFP" or "modified GFP") where what is intended would be obvious from the context." Thus, fluorescence of an amino acid sequence of SEQ ID NO:2 or homologous to SEQ ID NO:2 has one or more amino acids that have undergone oxidation and cyclization, so that the resulting fluorescent product may be termed a product of that amino acid sequence. Applicants submit that one of ordinary skill in the art would understand that a "fluorescent product of a modified form of an Aequorea wild-type GFP polypeptide" was an amino acid sequence having the requisite homology to an Aequorea wild-type GFP polypeptide and including one or more amino acids that have undergone oxidation and cyclization.

Accordingly, the claims not including the term objected to as allegedly unclear, applicants believe the rejections to Claims 1-15 under 35 U.S.C. §112, second paragraph, to be overcome.

The Double Patenting Rejections

Claims 1-15 have been rejected under the judicially created doctrine of obviousness double patenting, as allegedly being unpatentable over Claims 1-64 of U.S. Patent No. 5,777,079 and over Claims 1-5 of U.S. Patent No. 6,066,476.

Applicants traverse these rejections. However, in the interest of advancing the application towards issuance, a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) is filed with this response to overcome the rejections under the judicially created doctrine of obviousness double patenting over Claims 1-64 of U.S. Patent No. 5,777,079 and over Claims 1-5 of U.S. Patent No. 6,066,476.

The Objections to Claims 1, 13, and 14

Claims 1, 13 and 14 stand objected to as requiring minor typographical corrections. The requested typographical corrections having been made, applicants believe the objection to the claims to be overcome.

The Objections to the Specification

The sequences now bearing the identifiers "SEQ ID NO: 3," "SEQ ID NO:4" and "SEQ ID NO:5" were disclosed in the application as originally filed, at page 18, paragraph 53. With the enclosed amended sequence listing (both paper and computer-readable copies) and with the amendments to the specification, these sequences are now included in the sequence listing and identified by sequence identifier numbers.

The mistyping of the acronym "GFP" in the specification has been corrected.

Accordingly, Applicants believe the objection to the specification based on the sequence listing and mistyping to be overcome.

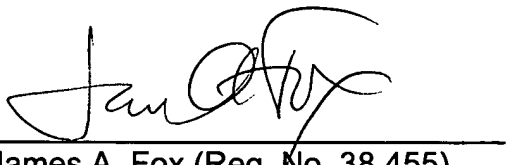
CONCLUSION

Applicants respectfully submit that the rejections of Claims 1-15 are overcome, that all claims are in condition for allowance, and request reconsideration and allowance of all pending claims. The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** citing Attorney's Docket No. **39754-0861 CPDV3C1**.

Respectfully submitted,

Date: December 19, 2003

By: 
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